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Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis

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ABSTRACT

BACKGROUND

BG-12 (dimethyl fumarate) is in development as an oral treatment for relapsing–remitting multiple sclerosis, which is commonly treated with parenteral agents (interferon or glatiramer acetate).

METHODS

In this phase 3, randomized study, we investigated the efficacy and safety of oral BG-12, at a dose of 240 mg two or three times daily, as compared with placebo in patients with relapsing–remitting multiple sclerosis. An active agent, glatiramer acetate, was also included as a reference comparator. The primary end point was the annualized relapse rate over a period of 2 years. The study was not designed to test the superiority or noninferiority of BG-12 versus glatiramer acetate.

RESULTS

At 2 years, the annualized relapse rate was significantly lower with twice-daily BG-12 (0.22), thrice-daily BG-12 (0.20), and glatiramer acetate (0.29) than with placebo (0.40) (relative reductions: twice-daily BG-12, 44%, P<0.001; thrice-daily BG-12, 51%, P<0.001; glatiramer acetate, 29%, P=0.01). Reductions in disability progression with twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate versus placebo (21%, 24%, and 7%, respectively) were not significant. As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the numbers of new or enlarging T_2-weighted hyperintense lesions (all P<0.001) and new T_1-weighted hypointense lesions (P<0.001, P<0.001, and P=0.002, respectively). In post hoc comparisons of BG-12 versus glatiramer acetate, differences were not significant except for the annualized relapse rate (thrice-daily BG-12), new or enlarging T_2-weighted hyperintense lesions (both BG-12 doses), and new T_1-weighted hypointense lesions (thrice-daily BG-12) (nominal P<0.05 for each comparison). Adverse events occurring at a higher incidence with an active treatment than with placebo included flushing and gastrointestinal events (with BG-12) and injection-related events (with glatiramer acetate). There were no malignant neoplasms or opportunistic infections reported with BG-12. Lymphocyte counts decreased with BG-12.

CONCLUSIONS

In patients with relapsing–remitting multiple sclerosis, BG-12 (at both doses) and glatiramer acetate significantly reduced relapse rates and improved neuroradiologic outcomes relative to placebo. (Funded by Biogen Idec; CONFIRM ClinicalTrials.gov number, NCT00451451.)

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Multiple sclerosis is a chronic demyelinating and neurodegenerative disease of the central nervous system, which is commonly treated with parenteral agents (interferon beta and glatiramer acetate). Oxidative stress and proinflammatory stimuli are important pathologic factors in multiple sclerosis.[1-3] Experimental data suggest that BG-12, an oral formulation of dimethyl fumarate, has antiinflammatory and cytoprotective properties that are mediated through activation of the nuclear factor (erythroid-derived 2)–like 2 transcriptional pathway, among others.[3-6]

Here, we report the results of the Comparator and an Oral Fumarate in Relapsing–Remitting Multiple Sclerosis (CONFIRM) trial, a randomized, multicenter, double-blind, 2-year study evaluating the efficacy and safety of BG-12, at a dose of 240 mg two or three times per day, versus placebo in patients with relapsing–remitting multiple sclerosis. A rater-blinded, active agent approved for relapsing–remitting multiple sclerosis (subcutaneous glatiramer acetate at a dose of 20 mg per day) was also included as a reference comparator, to allow a relative benefit–risk assessment of BG-12 through comparison of the active-treatment groups with the placebo group.

Methods

Study Oversight

The study was approved by central and local ethics committees and conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice[7] and the Declaration of Helsinki.[8] An advisory committee participated in study design and oversight of study conduct, a data and safety monitoring committee reviewed all pertinent benefit–risk data, and an independent neurologic evaluation committee, whose members were unaware of the study-group assignments, provided confirmation of relapses of multiple sclerosis (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Data were gathered by the investigators and were analyzed by the sponsor (Biogen Idec), and data remained confidential during the study. All the authors were involved in all stages of manuscript development and vouch for the completeness and accuracy of the data. The first draft was cowritten by the first and last authors (the latter is a representative of the sponsor), with assistance from a medical-communications agency paid by the sponsor. The study was conducted in accordance with the study protocol, which is available at NEJM.org.

Patients

Key eligibility criteria were a diagnosis of relapsing–remitting multiple sclerosis (McDonald criteria[9]), an age of 18 to 55 years, a score of 0 to 5 on the Expanded Disability Status Scale (EDSS, which ranges from 0 to 10, with higher scores indicating greater disability),[10] and at least one clinically documented relapse in the previous 12 months or at least one gadolinium-enhancing lesion 0 to 6 weeks before randomization. Key exclusion criteria were progressive forms of multiple sclerosis,[11] other clinically significant illness, prespecified laboratory abnormalities, and prior exposure to glatiramer acetate or contraindicated medications (see the Supplementary Appendix for additional details).

Patients were informed of approved therapies[12] for multiple sclerosis, and they provided written informed consent. Reconsent was required after a confirmed relapse or confirmed disability progression.

Study Design

Patients at 200 sites in 28 countries were randomly assigned in a 1:1:1:1 ratio to receive oral placebo, BG-12 at a dose of 240 mg two times daily, BG-12 at a dose of 240 mg three times daily, or subcutaneous daily injections of 20 mg of glatiramer acetate for 96 weeks (Fig. S1 in the Supplementary Appendix). Patients receiving glatiramer acetate were aware of their treatment assignment. All study management and site personnel, investigators, and patients were unaware of assignment to the BG-12 and placebo groups; examining neurologists, technicians at the magnetic resonance imaging (MRI) reading center, and members of the independent neurologic evaluation committee were unaware of all study-group assignments. Each site used separate examining and treating neurologists, thereby maintaining rater blinding for all study groups, including the group that received glatiramer acetate. To ensure that the assignments to the BG-12 and placebo groups would not be revealed, patients in those groups were instructed not to take the study medication within 4 hours before each study visit, since a flushing reaction is known to be more common with BG-12.[13] Patients could switch to an alternative medication

for multiple sclerosis if they had two confirmed relapses and had completed 48 weeks of study treatment or if they had confirmed disability progression (see the Supplementary Appendix).

STUDY PROCEDURES AND END POINTS

Standardized neurologic assessments, including an EDSS assessment, were performed every 12 weeks and at the time of suspected relapse (evaluated during unscheduled visits). MRI scans were obtained in a subset of patients at sites with MRI capabilities, at screening and at weeks 24, 48, and 96, and were evaluated in a blinded manner at a central MRI reading center.

The primary efficacy end point was the annualized relapse rate at 2 years, based on protocol-defined relapses (new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, accompanied by new objective neurologic findings, and separated from the onset of other confirmed relapses by at least 30 days) that were confirmed by the independent neurologic evaluation committee. Secondary efficacy end points included the number of new or enlarging hyperintense lesions on T_2-weighted images, the number of new hypointense lesions on T_1-weighted images, the proportion of patients with a relapse, and the time to disability progression, each at 2 years. Disability progression was defined as an increase in the EDSS score of at least 1.0 point in patients with a baseline score of 1.0 or more or an increase of at least 1.5 points in patients with a baseline score of 0, confirmed at least 12 weeks later. Tertiary end points included a comparison of the relative benefits and risks of BG-12 or glatiramer acetate versus placebo and the number of gadolinium-enhancing lesions at 2 years (see the Supplementary Appendix).

STATISTICAL ANALYSIS

We estimated that a sample of 308 patients per group would provide approximately 84% power at a two-sided significance level of 0.05 to detect a 25% relative reduction in the 2-year annualized relapse rate, with the assumption of an annualized relapse rate of 0.61 in the placebo group. A sequential (closed) testing procedure was used to control for overall type I error due to multiple comparisons (see the Supplementary Appendix).

Primary and secondary end points were analyzed in the intention-to-treat (ITT) population (all randomly assigned patients who received study treatment) and in the MRI cohort (patients in the ITT population for whom any postbaseline MRI data were available), with the use of two-sided statistical tests at a significance level of 0.05.

The annualized relapse rate (total number of relapses divided by patient-years in the study, excluding data obtained after patients switched to alternative multiple sclerosis medications) was analyzed with the use of a negative binomial regression model adjusted for baseline EDSS score, age, region (regions were defined on the basis of not only geography but also the type of health care system and access to health care in each country), and number of relapses in the 12 months before study entry. Four sensitivity analyses were performed (see the Supplementary Appendix).

Negative binomial regression was used for analysis of the total number of new or enlarging hyperintense lesions on T_2-weighted images and the total number of new hypointense lesions on T_1-weighted images at 2 years. A Cox proportional-hazards model was used for analysis of the proportion of patients with clinical relapse and the time to disability progression. Models were adjusted for region, EDSS score, age, relapse rate, and volume of lesions, as appropriate.

In general, analyses of primary and secondary end points were based on all observed data before patients switched to alternative multiple sclerosis medications, with analyses of MRI end points additionally based on missing data imputed with the use of a constant-rate assumption. The study was not designed to test the superiority or noninferiority of BG-12 versus glatiramer acetate. Safety was analyzed with the use of descriptive statistics for the safety population (all patients who received at least one dose of the study medication), excluding data obtained after patients switched to alternative multiple sclerosis medications.

RESULTS

PATIENTS

Of 1430 randomly assigned patients, 1417 were included in the ITT population (Fig. S2 in the Supplementary Appendix). Baseline demographic and disease characteristics were similar among the four study groups (Table 1) and between the MRI cohort (681 patients) (Table S1 in the Supplementary Appendix) and non-MRI cohort (736 patients). Approximately 29% of patients had re-

Table 1. Baseline Demographic and Disease Characteristics (ITT Population).*

Characteristic	Placebo (N=363)	Twice-Daily BG-12 (N=359)	Thrice-Daily BG-12 (N=345)†	Glatiramer Acetate (N=350)†
Age — yr	36.9±9.2	37.8±9.4	37.8±9.4	36.7±9.1
Female sex — no. (%)	251 (69)	245 (68)	250 (72)	247 (71)
Weight — kg	72.6±16.9	71.9±17.9	72.5±17.8	71.4±19.1
Race — no. (%)‡				
White	305 (84)	304 (85)	292 (85)	290 (83)
Asian	28 (8)	28 (8)	26 (8)	25 (7)
Black	9 (2)	2 (<1)	5 (1)	11(3)
Other or unknown	21 (6)	25 (7)	22 (6)	24 (7)
Time since diagnosis — yr	4.8±5.0	4.9±5.1	4.6±5.2	4.4±4.7
Any prior approved DMT — no. (%)§	111 (31)	101 (28)	100 (29)	103 (29)
Relapses in previous 12 mo — no.	1.4±0.8	1.3±0.6	1.4±0.7	1.4±0.6
EDSS score at baseline — no. (%)¶				
0	13 (4)	15 (4)	15 (4)	18 (5)
1.0 or 1.5	78 (21)	85 (24)	84 (24)	77 (22)
2.0 or 2.5	111 (31)	94 (26)	94 (27)	96 (27)
3.0 or 3.5	98 (27)	105 (29)	99 (29)	99 (28)
4.0 or 4.5	50 (14)	47 (13)	42 (12)	46 (13)
5.0	13 (4)	12 (3)	11 (3)	14 (4)
Mean score on EDSS¶	2.6±1.2	2.6±1.2	2.5±1.2	2.6±1.2

* All baseline characteristics were well balanced among the study groups (nominal P>0.05). Plus–minus values are means ±SD. DMT denotes disease-modifying therapy, EDSS Expanded Disability Status Scale, and ITT intention to treat.
† One patient randomly assigned to the thrice-daily BG-12 group took glatiramer acetate throughout the study. This patient was counted in the thrice-daily BG-12 group of the ITT population and in the glatiramer acetate group of the safety population.
‡ Race was self-reported.
§ Prior exposure to interferon beta-1a (in 21% of the ITT population), interferon beta-1b (11%), natalizumab (1%), and glatiramer acetate (<1%) was balanced across groups; one patient was randomly assigned to glatiramer acetate who had previously been exposed to the drug. Patients may have received more than one prior multiple sclerosis medication. Patients may also have received other, nonapproved therapies for multiple sclerosis (the proportion of patients receiving any multiple sclerosis medication before the study was 40 to 41% across study groups).
¶ Scores on the EDSS range from 0 to 10, with higher scores indicating a greater degree of disability. One patient in the twice-daily BG-12 group had a baseline score higher than 5.0.

ceived an approved disease-modifying therapy before study entry.

Study completion rates were similar across study groups (overall rate in the ITT population, 80%), with a mean time in the study of 86.1, 84.4, 84.1, and 88.5 weeks in the placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively. The rate of study-drug discontinuation was higher in the placebo group than in the other groups (36% vs. 30% in the twice-daily BG-12 group, 28% in the thrice-daily BG-12 group, and 25% in the glatiramer acetate group) (Table S2 in the Supplementary Appendix), as was the proportion of patients who switched to alternative multiple sclerosis medications (11% vs. 7%, 8%, and 6%, respectively).

EFFICACY

Clinical End Points

The frequency of relapses of multiple sclerosis was significantly reduced by twice-daily and thrice-daily BG-12, with an adjusted annualized relapse rate at 2 years (primary end point) of 0.22 and 0.20, respectively, representing reductions relative to placebo (annualized relapse rate, 0.40) of 44% and 51% (P<0.001 for both comparisons). Glatiramer acetate also reduced the annualized relapse rate (0.29; relative reduction, 29% vs. placebo;

P=0.01) (Fig. 1A and Table 2). Similar results were obtained in four sensitivity analyses that used different definitions of relapse or that included data after patients switched to alternative medications, findings that show the robustness of the results for the primary end point (Fig. S3 in the Supplementary Appendix).

As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the risk of relapse, by 34% (P=0.002), 45% (P<0.001), and 29% (P=0.01), respectively (Table 2). The Kaplan–Meier estimate of the proportion of patients with a relapse at 2 years was 41% in the placebo group as compared with 29%, 24%, and 32% in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively (Fig. S4 in the Supplementary Appendix). Similar findings were observed in sensitivity analyses (Fig. S5 in the Supplementary Appendix).

Disability progression was not significantly reduced with twice-daily BG-12, thrice-daily BG-12, or glatiramer acetate, as compared with placebo (relative reduction, 21% [P=0.25], 24% [P=0.20], and 7% [P=0.70], respectively) (Fig. 1B and Table 2). The Kaplan–Meier estimate of the proportion of patients with disability progression was 17% in the placebo group as compared with 13%, 13%, and 16% in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively. In a preplanned sensitivity analysis, 24-week confirmed disability progression was not significantly reduced versus placebo in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups (38% [P=0.06], 33% [P=0.12], and 13% [P=0.55], respectively), with an estimated proportion of patients with disability progression of 13% in the placebo group versus 8%, 9%, and 11% in the twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate groups, respectively (Table S3 in the Supplementary Appendix).

MRI End Points

As compared with placebo, twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate significantly reduced the mean number of new or enlarging hyperintense lesions on T_2-weighted images at 2 years, by 71%, 73%, and 54%, respectively (P<0.001 for all comparisons) (Table 2, and Fig. S6A in the Supplementary Appendix), and reduced the mean number of new hypointense lesions on T_1-weighted images, by 57% (P<0.001), 65% (P<0.001), and 41% (P=0.002), respectively (Table 2, and Fig. S6B in the Supplementary Appendix). The percentage of patients free from new or enlarging hyperintense lesions on T_2-weighted images at 2 years was higher with twice-daily BG-12 (27%), thrice-daily BG-12 (31%), or glatiramer acetate (24%) than with placebo (12%); corresponding percentages free from new hypointense lesions on T_1-weighted images were 39%, 44%, and 34% versus 21%.

The odds of having more gadolinium-enhancing lesions at 2 years was also significantly reduced by twice-daily BG-12, thrice-daily BG-12, and glatiramer acetate treatment as compared with placebo, by 74%, 65%, and 61%, respectively (P<0.001 for all comparisons) (Table 2, and Fig. S6C in the Supplementary Appendix).

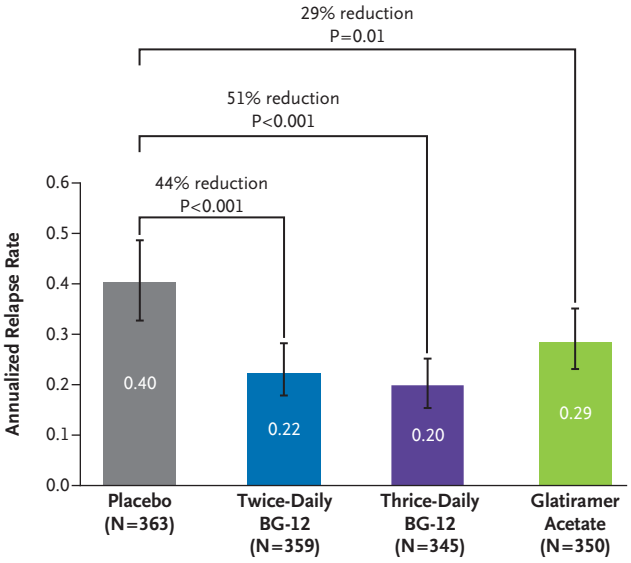
Benefits and Risks of BG-12 versus Glatiramer Acetate

In the prespecified comparison of the relative efficacy of each active treatment with placebo, the estimated treatment effects of both doses of BG-12 were numerically similar to or larger than those of glatiramer acetate across efficacy end points (Table 2). In a post hoc direct evaluation of the relative benefit of BG-12 versus glatiramer acetate, estimates and 95% confidence intervals excluded unity for some comparisons (Fig. S7 in the Supplementary Appendix). Nominal P values for comparisons of twice-daily BG-12 and thrice-daily BG-12 with glatiramer acetate were as follows: annualized relapse rate, P=0.10 and P=0.02, respectively; new or enlarging hyperintense lesions on T_2-weighted images, P=0.007 and P=0.002; new hypointense lesions on T_1-weighted images, P=0.08 and P=0.003; proportion of patients with a relapse, P=0.58 and P=0.09; and time to disability progression, P=0.44 and P=0.37.

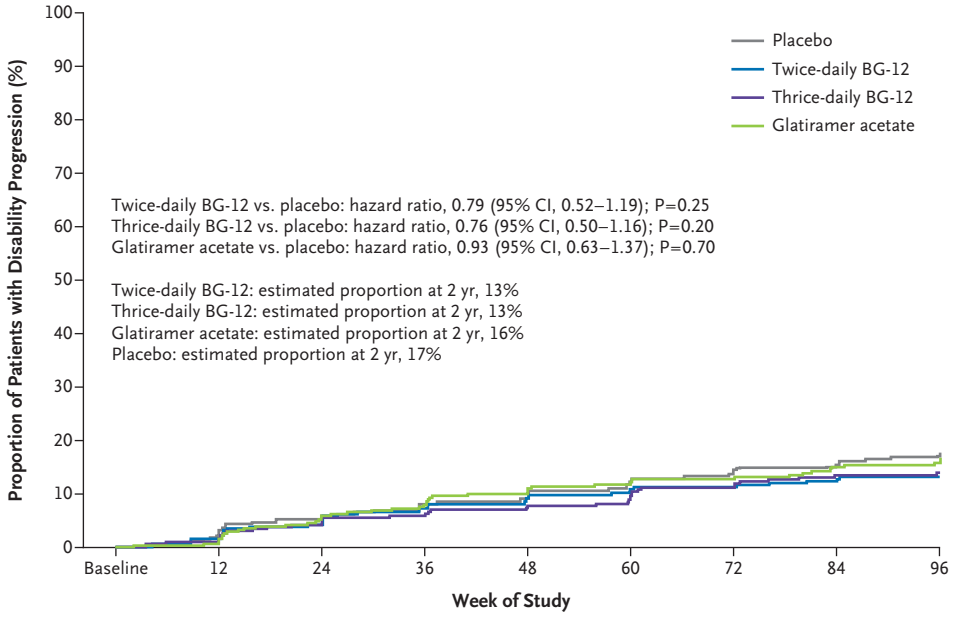
SAFETY

The overall incidence of adverse events was similar across study groups (87 to 94%) (Table 3). Adverse events reported more frequently with BG-12 than with placebo included flushing, gastrointestinal events (diarrhea, nausea, and upper abdominal pain), upper respiratory tract infections, and erythema. For flushing, which included events of flushing and hot flush, the incidence was 35% with twice-daily BG-12 and 28% with thrice-daily BG-12 versus 6% with placebo and 3% with glatiramer acetate; for gastrointestinal events, the incidence was 36% with twice-daily BG-12

A Annualized Relapse Rate



B Time to 12-Wk Confirmed Disability Progression



No. at Risk									
Placebo	363	339	317	297	273	254	235	228	149
Twice-daily BG-12	359	323	302	283	270	263	257	249	146
Thrice-daily BG-12	345	309	287	277	269	262	249	238	159
Glatiramer acetate	350	326	307	291	279	269	262	249	178

Figure 1. Clinical Outcomes at 2 Years in the Intention-to-Treat Population.

Annualized relapse rates (Panel A) were calculated with the use of a negative binomial regression model, with adjustment for baseline score (≤2.0 vs. >2.0) on the Expanded Disability Status Scale (EDDS, which ranges from 0 to 10, with higher scores indicating a greater degree of disability), baseline age (<40 years vs. ≥40 years), region (regions were defined on the basis of not only geography but also the type of health care system and access to health care in each country), and number of relapses in the 12 months before study entry. Relapses were confirmed by an independent neurologic evaluation committee. The I bars indicate 95% confidence intervals. Hazard ratios for time to disability progression (Panel B) were calculated with the use of a Cox proportional-hazards model, with adjustment for baseline EDSS score, baseline age (<40 years vs. ≥40 years), and region. The estimated proportions of patients with disability progression at 2 years are Kaplan–Meier estimates.

Table 2. Clinical End Points (ITT Population) and MRI End Points (MRI Cohort) during the Study.*

End Point	Placebo (N=363)	Twice-Daily BG-12 (N=359)	Thrice-Daily BG-12 (N=345)	Glatiramer Acetate (N=350)
Annualized relapse rate at 2 yr†				
Rate (95% CI)	0.40 (0.33–0.49)	0.22 (0.18–0.28)	0.20 (0.16–0.25)	0.29 (0.23–0.35)
Percentage reduction vs. placebo (95% CI)		44.0 (26.0–57.7)‡	50.5 (33.8–63.1)‡	28.6 (6.9–45.2)§
Time to first confirmed relapse, 25th percentile — wk¶	30	72	NA‖	57
Estimated proportion of patients with a relapse at 2 yr				
Proportion — %¶	41	29	24	32
Hazard ratio vs. placebo (95% CI)**		0.66 (0.51–0.86)††	0.55 (0.42–0.73)‡	0.71 (0.55–0.92)††
Disability progression at 2 yr				
Estimated proportion of patients with progression confirmed at least 12 wk later — %¶	17	13	13	16
Hazard ratio vs. placebo (95% CI)‡‡		0.79 (0.52–1.19)	0.76 (0.50–1.16)	0.93 (0.63–1.37)
New or enlarging T_2-weighted hyperintense lesions at 2 yr§§				
No. of patients evaluated	139	140	140	153
Adjusted mean no. of lesions (95% CI)	17.4 (13.5–22.4)	5.1 (3.9–6.6)	4.7 (3.6–6.2)	8.0 (6.3–10.2)
Ratio of mean no. of lesions in active-treatment group to mean no. in placebo group (95% CI)		0.29 (0.21–0.41)‡	0.27 (0.20–0.38)‡	0.46 (0.33–0.63)‡
New T_1-weighted hypointense lesions at 2 yr§§				
No. of patients evaluated	139	140	140	154
Adjusted mean no. of lesions (95% CI)	7.0 (5.3–9.2)	3.0 (2.3–4.0)	2.4 (1.8–3.2)	4.1 (3.2–5.3)
Ratio of mean no. of lesions in active-treatment group to mean no. in placebo group (95% CI)		0.43 (0.30–0.61)‡	0.35 (0.24–0.49)‡	0.59 (0.42–0.82)‡
Gadolinium-enhancing lesions at 2 yr§§				
No. of patients evaluated	144	147	144	161
No. of lesions	2.0±5.6	0.5±1.7	0.4±1.2	0.7±1.8
Odds ratio vs. placebo (95% CI)		0.26 (0.15–0.46)‡	0.35 (0.20–0.59)‡	0.39 (0.24–0.65)‡

* Plus–minus values are means ±SD. CI denotes confidence interval, and NA not available.
† Annualized relapse rates were calculated on the basis of negative binomial regression, with adjustment for baseline EDSS score (≤2.0 vs. >2.0), baseline age (<40 years vs. ≥40 years), region (regions were defined on the basis of not only geography but also the type of health care system and access to health care in each country), and number of relapses in the 12 months before study entry. Relapses were confirmed by an independent neurologic evaluation committee.
‡ P<0.001.
§ P<0.05.
¶ Values were calculated with the use of the Kaplan–Meier product-limit method.
‖ The exact estimate was not available because the 25th percentile was greater than 96 weeks.
** Hazard ratios were calculated with the use of a Cox proportional-hazards model, with adjustment for baseline EDSS score (≤2.0 vs. >2.0), baseline age (<40 years vs. ≥40 years), region, and number of relapses in the 12 months before study entry.
†† P≤0.01.
‡‡ Hazard ratios were calculated with the use of a Cox proportional-hazards model, with adjustment for baseline EDSS score as a continuous variable, region, and baseline age (<40 years vs. ≥40 years).
§§ Patients who were evaluated were patients in the MRI cohort with postbaseline data. Missing data before the use of alternative multiple sclerosis medications and visits after patients switched to alternative multiple sclerosis medications were imputed with the use of a constant-rate assumption. Ratios, relative reductions, 95% CIs, and P values were calculated with the use of negative binomial regression for new T_2-weighted and new T_1-weighted lesions and ordinal logistic regression for gadolinium-enhancing lesions, with adjustment for region and baseline T_2-weighted lesion volume, T_1-weighted lesion volume, or number of gadolinium-enhancing lesions, as appropriate.

and 41% with thrice-daily BG-12 versus 26% with placebo and 15% with glatiramer acetate. Flushing and gastrointestinal events were of mild or moderate severity for most patients; the incidence of these events was highest in the first month of the study, decreasing thereafter (Fig. S8 in the Supplementary Appendix). Adverse events reported more frequently in the glatiramer acetate group than in the placebo group were injection-related events: injection-site pain (placebo, 0%; glatiramer acetate, 8%) and injection-site erythema (placebo, 0%; glatiramer acetate, 9%).

Table 3. Adverse Events (Safety Population).

Event	Placebo (N=363)	Twice-Daily BG-12 (N=359)	Thrice-Daily BG-12 (N=344)*	Glatiramer Acetate (N=351)*
	number of patients (percent)			
Any adverse event	333 (92)	338 (94)	316 (92)	304 (87)
Most common adverse events†				
Multiple sclerosis relapse	155 (43)	110 (31)	85 (25)	119 (34)
Flushing‡	13 (4)	110 (31)	83 (24)	6 (2)
Nasopharyngitis	58 (16)	62 (17)	63 (18)	51 (15)
Headache	49 (13)	52 (14)	46 (13)	46 (13)
Diarrhea‡	28 (8)	45 (13)	50 (15)	14 (4)
Urinary tract infection	42 (12)	52 (14)	41 (12)	46 (13)
Nausea‡	29 (8)	40 (11)	51 (15)	15 (4)
Upper respiratory tract infection‡	34 (9)	36 (10)	47 (14)	27 (8)
Back pain	33 (9)	35 (10)	36 (10)	32 (9)
Fatigue	33 (9)	37 (10)	33 (10)	30 (9)
Upper abdominal pain‡	17 (5)	36 (10)	33 (10)	4 (1)
Proteinuria	25 (7)	29 (8)	35 (10)	30 (9)
Depression	35 (10)	24 (7)	15 (4)	30 (9)
Adverse events leading to study-drug discontinuation	38 (10)	44 (12)	41 (12)	35 (10)
Death§	1 (<1)	0	1 (<1)	1 (<1)
Any serious adverse event	79 (22)	61 (17)	54 (16)	60 (17)
Most common serious adverse events¶				
Multiple sclerosis relapse	51 (14)	39 (11)	30 (9)	36 (10)
Gastroenteritis	0	2 (<1)	2 (<1)	0
Cellulitis	0	2 (<1)	1 (<1)	0
Abdominal pain	0	2 (<1)	0	0
Back pain	0	2 (<1)	0	0
Muscle strain	0	0	2 (<1)	0
Depression	0	0	1 (<1)	2 (<1)
Spontaneous abortion	2 (<1)	0	0	0
Anaphylactic reaction	0	0	0	2 (<1)
Convulsion	2 (<1)	0	0	0
Pneumonia	1 (<1)	0	0	2 (<1)

* One patient randomly assigned to the thrice-daily BG-12 group and included in the BG-12 group of the ITT population took glatiramer acetate throughout the study and was therefore counted in the glatiramer acetate group of the safety population.
† These events were reported by at least 10% of patients in any group. The events are listed by decreasing incidence among BG-12–treated patients.
‡ These events had a reported incidence at least 5 percentage points higher in any active treatment group than in the placebo group.
§ Deaths occurring during the study or within 30 days after study withdrawal were due to stroke (placebo group), complications after a multiple sclerosis relapse (thrice-daily BG-12 group), and suicide (glatiramer acetate group).
¶ These events were reported by at least two patients in any group. The events are listed by decreasing incidence among BG-12–treated patients.

Infections were reported in 56% of patients in both BG-12 groups and 50% of patients in the placebo and glatiramer acetate groups. Infections with an incidence that was at least 2 percentage points higher in either BG-12 group than in the placebo group included nasopharyngitis, urinary tract infection, upper respiratory tract infection, bronchitis, sinusitis, and gastroenteritis. The inci-

dence of serious infections was low and similar (1 to 2%) across groups; no opportunistic infections were reported in any group.

Overall, the incidence of adverse events leading to discontinuation of the study drug was similar across groups (10% in the placebo group, 12% in both BG-12 groups, and 10% in the glatiramer acetate group) (Table S4 in the Supplementary Appendix); discontinuation due to a multiple sclerosis relapse was more frequent in the placebo group (5%) than in the twice-daily BG-12 group (2%), thrice-daily BG-12 group (<1%), or glatiramer acetate group (2%). Aside from relapses, the only individual adverse events leading to discontinuation of the study drug in more than 1% of patients in any group were flushing (4% in the twice-daily BG-12 group and 2% in the thrice-daily BG-12 group) and nausea and diarrhea (2% each in the thrice-daily BG-12 group).

The incidence of serious adverse events was also similar across groups (Table 3). With the exception of relapses (which were more common in the placebo group than in the other groups), no individual serious adverse event was reported in more than two patients in any group. No malignant neoplasms were reported in the BG-12 groups; one malignant neoplasm was reported in the placebo group (breast neoplasm), and four malignant neoplasms were reported in the glatiramer acetate group (basal-cell carcinoma, cervical carcinoma, endometrial cancer, and thyroid cancer). The incidences of renal, hepatic, and cardiovascular events were similar across the four study groups.

In laboratory assessments, mean white-cell and lymphocyte counts in both BG-12 groups decreased during the first year and then plateaued, remaining within the normal range (Fig. S9 in the Supplementary Appendix). Mean percentage reductions from baseline in white-cell and lymphocyte counts were approximately 12% and 32%, respectively, in the twice-daily BG-12 group and 11% and 28% in the thrice-daily BG-12 group at 1 year. White-cell counts of less than 3.0×10^9 per liter and lymphocyte counts of less than 0.5×10^9 per liter (corresponding to National Cancer Institute Common Toxicity Criteria grade 2 or higher and 3 or higher, respectively) were seen in 10% and 5%, respectively, of patients in the twice-daily BG-12 group and in 7% and 4% of patients in the thrice-daily BG-12 group, versus 1% and less than 1% of patients in the placebo group. One patient in the thrice-daily BG-12 group discontinued treatment because of an adverse event associated with a low or decreased white-cell count; no patients in any group discontinued treatment because of an event associated with a low or decreased lymphocyte count. The incidence of liver aminotransferase levels that were at least three times the upper limit of the normal range was similar across the study groups; none of these elevations were concurrent with bilirubin levels that were more than two times the upper limit of the normal range (Table S5 in the Supplementary Appendix).

DISCUSSION

The CONFIRM study showed that in patients with relapsing–remitting multiple sclerosis, BG-12 at a dose of 240 mg two or three times daily, as compared with placebo, significantly reduced the rate of relapse, the proportion of patients with a relapse, and disease activity as measured by a range of MRI end points. These efficacy results are consistent with the results of previous BG-12 studies[14-16] and the Determination of the Efficacy and Safety of Oral Fumarate in Relapsing–Remitting MS (DEFINE) trial, reported in this issue of the *Journal*, a placebo-controlled, phase 3 study in which twice-daily and thrice-daily BG-12 reduced the annualized relapse rate by 53% and 48%, respectively, as compared with placebo and reduced the estimated proportion of patients with a relapse from 46% with placebo to 27% and 26%, respectively.[17] Similarly, there were fewer multiple sclerosis lesions on MRI scans in patients who received BG-12 than in those who received placebo, in both the CONFIRM and DEFINE studies. Although both doses of BG-12 had a significant effect on disability progression in the DEFINE study, neither BG-12 (at either dose) nor glatiramer acetate had a significant effect on disability progression in the CONFIRM study. A potential contributor to the difference in findings is that in the CONFIRM study, the proportion of patients with disability progression in the placebo group (17%) was lower than that in the DEFINE study (27%).[17] BG-12 treatment also resulted in a substantial decrease in the number of new hypointense lesions on T_1-weighted images, which are characterized by greater axonal loss than isointense lesions on T_1-weighted images.[18] This find-

ing suggests that BG-12 can reduce axonal loss, an important pathologic substrate of irreversible disability in multiple sclerosis.

These efficacy findings were accompanied by broadly similar incidences of adverse events, adverse events leading to discontinuation of the study drug, and serious adverse events across all four study groups. The most common adverse events associated with BG-12 treatment were flushing and gastrointestinal events, which were reported as mild or moderate in severity by most patients; the incidence of these events decreased over time. BG-12 was not associated with an increased risk of serious infections, opportunistic infections, or malignant neoplasms. The safety profile of BG-12 in the CONFIRM study was similar to that observed in the DEFINE study.

Although our study was not designed to test the superiority or noninferiority of BG-12 to glatiramer acetate, nominal P values for the post hoc direct comparison revealed a significantly greater treatment effect of BG-12 with respect to the annualized relapse rate (with thrice-daily BG-12), the number of new or enlarging hyperintense lesions on T_2-weighted images (with both BG-12 doses), and the number of new hypointense lesions on T_1-weighted images (with thrice-daily BG-12); none of the other comparisons with glatiramer acetate were significant. Furthermore, our findings with respect to the efficacy and safety of glatiramer acetate were generally consistent with of the results of previous studies of the drug in relapsing–remitting multiple sclerosis.[19-22]

Preclinical studies have shown that dimethyl fumarate, through induction of the Nrf2 pathway, both reduces inflammatory responses and provides protection against oxidative stress–induced injury.[3,23,24] These mechanisms may contribute to the beneficial effects observed in patients with relapsing–remitting multiple sclerosis, including reductions in clinical relapses and MRI measures of disease activity with BG-12 in comparison with placebo, in both the CONFIRM and DEFINE phase 3 studies. Overall, these findings support BG-12 as a potential initial oral treatment for patients with relapsing–remitting multiple sclerosis or as an alternative to currently available therapies.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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